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# CONTENTS

**Research on a novel alcohol-free CPC mouthrinse for the control of plaque and gingivitis**

Research Article

# A 6-month clinical trial to study the effects of a cetylpyridinium chloride mouthrinse on gingivitis and plaque

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ABSTRACT: ***Purpose***: To evaluate the effects of a novel mouthrinse containing 0.07% high bioavailable cetylpyridinium chloride (Crest Pro-Health Rinse) on the development of gingivitis and plaque *versus* a placebo control over a period of 6 months. ***Methods***: This was a randomized, 6-month, placebo-controlled, parallel groups, double blind, single center clinical trial. One hundred thirty-nine generally healthy adults with mild-to-moderate gingivitis were enrolled in the study. Subjects were given Modified Gingival Index (MGI), Gingival Bleeding Index (GBI) and Modified Quigley-Hein Plaque Index (MQH) examinations followed by a dental prophylaxis. Subjects were then randomly assigned to either the cetylpyridinium chloride (CPC) rinse or placebo rinse and instructed to begin rinsing twice a day with 20 ml of their assigned mouthrinse for 30 seconds after brushing their teeth. Subjects were assessed for MGI, GBI and MQH scores after 3 and 6 months of product use. Oral hard and soft tissue examinations were also performed at all visits. ***Results***: 124 subjects were evaluable at Month 3 and 119 at Month 6. After 6 months, subjects rinsing with the CPC rinse showed 15.4% less gingival inflammation, 33.3% less gingival bleeding, and 15.8% less plaque relative to the placebo group. All reductions were highly statistically significantly different ($P < 0.01$). Results were similar at 3 months. Both treatments were well-tolerated. (*Am J Dent* 2005;18: 9A-14A).

CLINICAL SIGNIFICANCE: This study demonstrates that the Crest Pro-Health 0.07% CPC mouthrinse provided significant antiplaque and antigingivitis benefits when used twice daily for 6 months as an adjunct to toothbrushing.

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## Introduction

Plaque-induced gingivitis continues to be a major dental problem for adults, adolescents and children worldwide.[1-5] Studies have shown that dental plaque plays an important role in the development of gingivitis, which in turn can advance to periodontitis.[6] Furthermore, some studies suggest that individuals with certain systemic diseases may be at higher risk of developing periodontitis.[7]

The mechanical elimination of dental plaque is the basis of the prevention and the treatment of gingivitis and periodontitis. Prevention may be partially achieved by conscientious daily brushing and flossing to remove plaque that forms each day before inflammation occurs.[8] However, inefficient brushing and inadequate flossing by most people[9] can lead to an accumulation of plaque and ultimately gingivitis, particularly in areas that are difficult to reach. Using chemotherapeutic agents is one approach to help control plaque accumulation in these areas.

Antimicrobial toothpastes and mouthrinses have been investigated and marketed to provide additional anti-plaque/anti-gingivitis activity when used daily as an adjunct to a mechanical oral hygiene regimen.[10-14] Several clinical studies have demonstrated that the broad spectrum antimicrobial agent cetylpyridinium chloride (CPC) can help control supragingival plaque and gingivitis.[15-17] It has been reported, however, that the efficacy of CPC mouthrinses can be compromised by formulation excipients, such as emulsifiers, leading to situations where two CPC mouthwashes could contain the same level of CPC but differ significantly in their relative efficacy.[18] Taking this into account, the FDA Plaque Subcommittee reviewed extensive data on CPC and deemed it to be safe and efficacious for the treatment of plaque-induced gingivitis within a concentration range of 0.045% to 0.10% CPC when present in a high-bioavailable matrix (as defined by prescribed performance assays).[19]

Recently, a new CPC rinse was introduced (Crest Pro-Health Rinse®) that meets these FDA guidelines. The product delivers 0.07% CPC in a high-bioavailable, alcohol-free formulation. The present study was conducted to investigate the long-term antiplaque and antigingivitis benefits of the CPC rinse relative to a placebo rinse.

## Materials and Methods

*Study design* - This was a randomized, 6-month, placebo-controlled, double-blind, parallel groups, single-center gingivitis clinical trial conducted at Dental Products Testing, Inc., West Palm Beach, Florida. Both the research protocol and written informed consent were reviewed and approved by an institutional review board prior to study initiation.

At the baseline visit, subjects who had not brushed nor flossed their teeth after 10 p.m. the previous night were given examinations to assess oral hard and soft tissue status and to measure gingival inflammation (Modified Gingival Index, MGI), gingival bleeding (Gingival Bleeding Index, GBI) and dental plaque (Modified Quigley-Hein Plaque Index, MQH). Subjects then received an oral prophylaxis and were randomly assigned in approximately equal numbers to one of the two treatment groups, balancing for gender and baseline smoking status:

- Experimental alcohol-free 0.07% CPC mouthrinse (Crest Pro-Health Rinse®);
- Alcohol-free placebo mouthrinse.[a]

Subjects were instructed to brush twice daily as they normally do, rinse thoroughly with water and then rinse with 20 mL of their assigned mouthrinse for 30 seconds. Subjects

Table 1. Baseline demographics characteristics.

**Subjects included in the Month 3 analysis**

| Treatment | N | Age Mean ± SD | Age Range | Gender % Female | Smoking status % Smokers |
|---|---|---|---|---|---|
| Placebo rinse | 64 | 39.3 ± 12.83 | 18 – 65 | 78% | 19% |
| CPC rinse | 60 | 36.5 ± 9.13 | 19 – 62 | 75% | 15% |

| Treatment | N | Ethnicity % Black | % Caucasian | % Hispanic | % Other |
|---|---|---|---|---|---|
| Placebo rinse | 64 | 19% | 75% | 6% | 0% |
| CPC rinse | 60 | 15% | 63% | 18% | 4% |

**Subjects included in the Month 6 analysis**

| Treatment | N | Age Mean ± SD | Age Range | Gender % Female | Smoking status % Smokers |
|---|---|---|---|---|---|
| Placebo rinse | 62 | 39.5 ± 12.86 | 18 – 65 | 79% | 19% |
| CPC Rinse | 57 | 36.8 ± 9.09 | 19 – 62 | 74% | 16% |

| Treatment | N | Ethnicity % Black | % Caucasian | % Hispanic | % Other |
|---|---|---|---|---|---|
| Placebo rinse | 62 | 18% | 76% | 6% | 0% |
| CPC rinse | 57 | 16% | 63% | 18% | 4% |

were given a kit containing a commercial dentifrice with sodium monofluorophosphate (Colgate Cavity Protection[b]), two soft compact flat head toothbrushes (Oral-B[c]), dose cups, and their assigned mouthrinses at baseline and at 4-week intervals throughout the study. Subjects were given verbal and written instructions on product usage and instructed to use only the test products provided during the study. Subjects performed the first dosing in the presence of study personnel after they received their kits. All remaining product usages were unsupervised.

To preserve blinding, investigational products and kits were identical in their appearance. Subjects returned after 3 and 6 months for examinations to reevaluate all efficacy and safety parameters, including MGI, GBI, MQH and hard and soft tissue safety. Subjects and site personnel were blinded to treatment assignment.

*Study population* - One-hundred thirty-nine (139) subjects were enrolled in the study. Study subjects were generally healthy adult volunteers from 18-65 years of age. To participate in the study, subjects were required to have a minimum of 18 natural teeth, a baseline MGI score of at least 1.75 and not greater than 2.3, and a Turesky plaque score of at least 1.5. Prospective subjects with any of the following conditions were ineligible for participation: requirement for antibiotic pre-medication prior to dental procedures; use of antibiotic, anti-inflammatory or anti-coagulant therapy for 14 days prior to the baseline exam; diabetes; pregnancy; rampant caries; advanced periodontal disease; history of significant adverse events to oral hygiene products; or other medical conditions that the investigator deemed could compromise the evaluation of study results. All subjects provided written informed consent prior to participation.

At Month 6 the study population ranged in age from 18-65 years, with a mean (SD) age of 38.2 (11.25) years. Females accounted for 76% of participants. Seventy percent of subjects were Caucasian, 17% were Black, 12% were Hispanic, and 1% were of other ethnic origins. Eighteen percent of subjects at Month 6 were self-reported smokers (Table 1).

Table 2. Modified Gingival Index.

| Score | Description |
|---|---|
| 0 | Absence of inflammation; |
| 1 | Mild inflammation; slight change in color, little change in texture of any portion of but not the entire marginal or papillary gingival unit; |
| 2 | Mild inflammation; criteria as above but involving the entire marginal or papillary gingival unit; |
| 3 | Moderate inflammation; glazing, redness, edema, and/or hypertrophy of the marginal or papillary gingival unit; |
| 4 | Severe inflammation; marked redness, edema and/or hypertrophy of the marginal or papillary gingival unit, spontaneous bleeding, congestion or ulceration. |

Table 3. Gingival Bleeding Index as defined by Saxton & van der Ouderaa.[22]

| Score | Description |
|---|---|
| 0 | Absence of bleeding after 30 seconds; |
| 1 | Bleeding observed after 30 seconds; |
| 2 | Immediate bleeding observed. |

Table 4. Turesky Modification of Quigley-Hein Plaque Index.

| Score | Description |
|---|---|
| 0 | No plaque; |
| 1 | Isolated areas of plaque at gingival margin; |
| 2 | Thin band of plaque at gingival margin (≤ 1mm); |
| 3 | Plaque covering up to 1/3 of tooth surface; |
| 4 | Plaque covering 1/3 to 2/3 of tooth surface; |
| 5 | Plaque covering ≥ 2/3 of tooth surface. |

*Clinical assessment* - Gingivitis was scored at Baseline, Month 3, and Month 6 by the MGI on the buccal and lingual marginal gingivae and interdental papillae of all scorable teeth. (Table 2) MGI is slightly different from the Löe-Silness Gingival Index (GI) in that probing is not used to elicit bleeding and the scoring system for mild and moderate inflammation is redefined.[20] Previous studies comparing the two indices have demonstrated that MGI correlates significantly with GI.[21] Thus, MGI allows for noninvasive assessment of early and subtle visual changes in severity and extent of gingivitis.

Gingival bleeding was evaluated at Baseline, Month 3, and Month 6 according to the GBI as defined by Saxton & van der Ouderaa.[22] Each of three gingival areas (buccal, mesial, and lingual) of the teeth was probed, waiting approximately 30 seconds before recording the number of gingival units which bled using a 0-2 scale (Table 3). Measurement of plaque area was done at Baseline, Month 3, and Month 6 by the Turesky modification of the Quigley-Hein Plaque Index, which emphasizes plaque in contact with the gingiva, on six surfaces (distobuccal, midbuccal, mesiobuccal, distolingual, midlingual, and mesiolingual) of all scorable teeth after use of disclosing solution.[23] (Table 4).

Oral soft tissue assessments were conducted *via* a visual examination of the oral cavity and perioral area using a standard dental light, dental mirror, and gauze. Structures examined included the gingiva (free and attached), hard and soft palate, oropharynx/uvula, buccal mucosa, tongue, floor of the mouth, labial mucosa, mucobuccal/mucolabial folds, lips,

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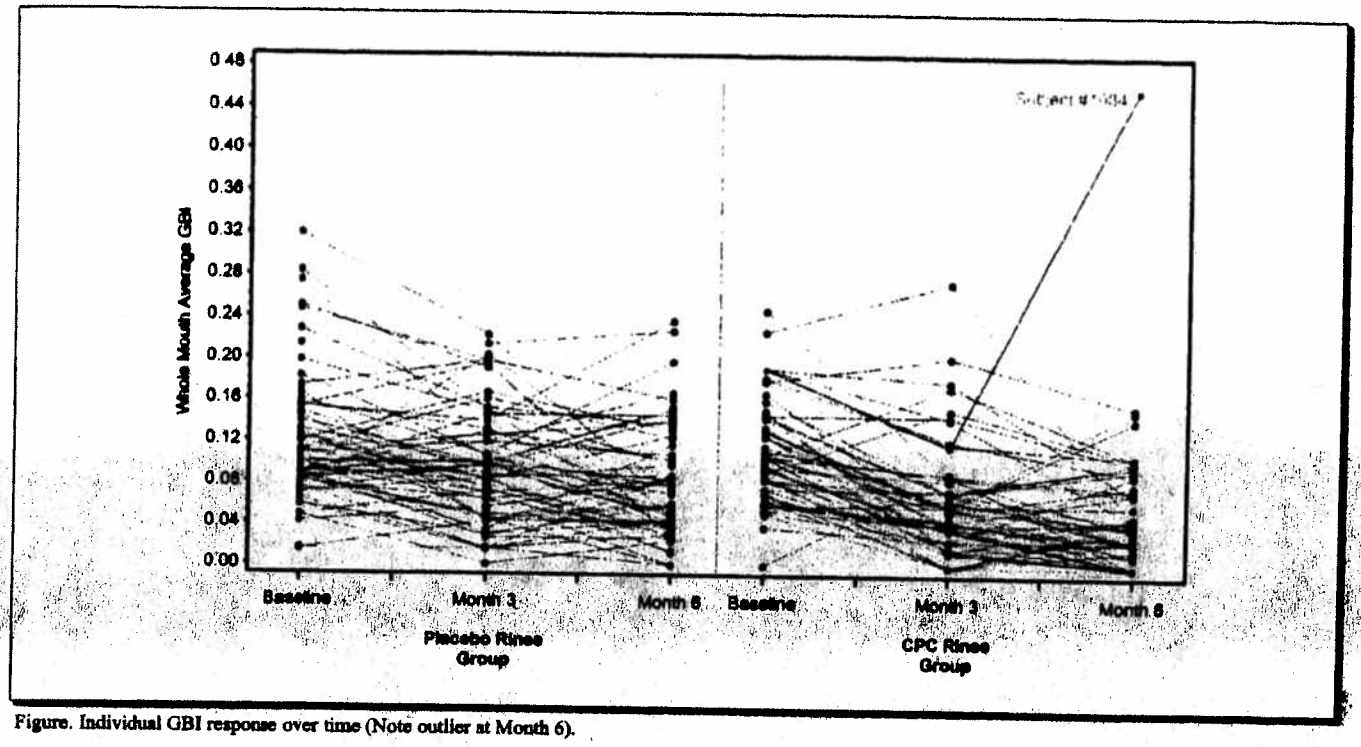


Figure. Individual GBI response over time (Note outlier at Month 6).

and perioral area. Oral hard tissues were assessed *via* a visual examination of the dentition and restorations utilizing a standard dental light, dental mirror, and air syringe. Abnormal oral soft/hard tissue findings noted after baseline or those that were present at baseline but worsened during investigational product usage were recorded as adverse events.

One examiner conducted MGI, GBI and safety examinations while a separate examiner assessed plaque. The same clinician performed the same measurements at all timepoints.

The whole-mouth average MGI, GBI and MQH scores were calculated for each subject at Baseline, Month 3 and Month 6 by summing the respective scores at each gradable site and dividing by the number of gradable sites. The proportion of sites bleeding was also calculated by summing the number of gradable sites with GBI scores of "1" or "2" and dividing by the number of gradable sites.

*Statistical analysis* - Descriptive summaries of the study population demographic data were prepared for subjects included in the Month 3 and Month 6 efficacy analyses. Evidence of imbalance across treatment groups was statistically assessed with two-sample *t*-tests and chi-squared tests.

Efficacy analyses were based on whole-mouth average MGI, GBI, and MQH scores, as well as the proportion of GBI sites bleeding. The 0.07% CPC rinse group was compared to the placebo rinse group with respect to each of these indices separately at Month 3 and Month 6. Analysis of covariance (ANCOVA) was to be used to model the post-baseline mean of each endpoint, using the respective baseline score as the covariate. The Month 3 and Month 6 data were to be modeled separately, with the Month 6 data of primary interest. The percent difference between treatments was to be calculated for each efficacy endpoint using the adjusted means from the ANCOVA models.

The ANCOVA efficacy analysis plan described above was executed, except for the Month 6 GBI data, where one subject (#1084) in the CPC rinse group was an extreme and influential outlier. As illustrated in the Figure, this subject's GBI score improved from Baseline to Month 3 but then reversed at Month 6 to more than double the value at Baseline. The studentized residual for this subject at Month 6 was 6.56, confirming that this score was an extreme outlier. No explanation for this subject's unusual Month 6 score could be found, either from a safety or compliance perspective. Given the fact that outliers can compromise the validity of traditional ANCOVA methods,[24,25] a rank ANCOVA that is robust to outliers was used to analyze the Month 6 GBI data.[26-28] Note that when the assumptions of ANCOVA are satisfied, *e.g.* no influential outliers, rank ANCOVA is less powerful (more conservative) than ANCOVA. However, when the assumptions of ANCOVA are not satisfied, *e.g.* influential outliers, rank ANCOVA results are more reliable than ANCOVA results. The percent benefit for the Month 6 GBI analysis was calculated using the median (robust to outliers) rather than the mean (not robust to outliers).

## Results

Of the 139 subjects who were randomized to treatment, 124 were present and evaluable at the Month 3 visit and 119 at the Month 6 visit. (One patient was late for the Month 6 examination and missed the gingivitis assessment.) There was no evidence (P> 0.05) of imbalance between groups with respect to age, gender, ethnicity or smoking habits at either Month 3 or Month 6 (Table 1).

*Modified Gingival Index* - The baseline mean MGI scores for subjects in the Month 3 analysis were 2.01 for the CPC rinse group and 2.02 for the placebo rinse group. At Month 3, the

Table 5. Modified Gingival Index results.

**Month 3 Analysis**

| Treatment | N | Baseline score (Mean ± SE) | Month 3 score (Adjusted Mean[a] ± SE) | % Reduction[b] |
|---|---|---|---|---|
| Placebo rinse | 64 | 2.02 ± 0.013 | 1.92 ± 0.026 | ------- |
| CPC rinse | 60 | 2.01 ± 0.014 | 1.68 ± 0.027 | 12.5% |

The adjusted means were statistically significantly different (P< 0.0001).

**Month 6 Analysis**

| Treatment | N | Baseline score (Mean ± SE) | Month 3 score (Adjusted Mean[a] ± SE) | % Reduction[b] |
|---|---|---|---|---|
| Placebo rinse | 62 | 2.02 ± 0.014 | 1.88 ± 0.038 | ------- |
| CPC rinse | 56 | 2.01 ± 0.013 | 1.59 ± 0.040 | 15.4% |

The adjusted means were statistically significantly different (P< 0.0001).
[a] Adjusted means and standard errors from analysis of covariance with baseline score as the covariate.
[b] % Reduction = 100% x (Placebo rinse mean – CPC rinse mean)/Placebo rinse mean.

Table 7. Proportion of bleeding sites results.

**Month 3 Analysis**

| Treatment | N | Baseline score (Mean ± SE) | Month 3 score (Adjusted Mean[a] ± SE) | % Reduction[b] |
|---|---|---|---|---|
| Placebo rinse | 64 | 0.106 ± 0.0067 | 0.084 ± 0.0049 | ------- |
| CPC rinse | 60 | 0.101 ± 0.0081 | 0.064 ± 0.0051 | 23.8% |

The adjusted means were statistically significantly different (P= 0.006).

**Month 6 Analysis**

| Treatment | N | Baseline score (Mean ± SE) | Month 3 score (Adjusted Mean[a] ± SE) | % Reduction[b] |
|---|---|---|---|---|
| Placebo rinse | 62 | 0.105 ± 0.0068 | 0.074 ± 0.0060 | ------- |
| CPC rinse | 56 | 0.096 ± 0.0055 | 0.050 ± 0.0063 | 32.4% |

The adjusted means were statistically significantly different (P= 0.007).
[a] Adjusted means and standard errors from analysis of covariance with baseline score as the covariate.
[b] % Reduction = 100% x (Placebo rinse mean – CPC rinse mean)/Placebo rinse mean.

adjusted mean score for the CPC rinse group was 12.5% lower than that of the placebo rinse group (1.68 *vs.* 1.92). The difference between groups was highly statistically significant (P< 0.0001) (Table 5).

The baseline mean MGI scores for subjects in the Month 6 analysis were 2.01 for the CPC rinse group and 2.02 for the placebo rinse group. At Month 6 the adjusted mean for the CPC rinse group was 15.4% lower than that of the placebo rinse group (1.59 *vs.* 1.88). The difference between groups was highly statistically significant (P< 0.0001) (Table 5).

*Gingival bleeding* - For subjects in the Month 3 analysis, the baseline mean GBI score for the CPC rinse group was 0.114 compared to 0.122 for the placebo rinse group. At Month 3 the adjusted mean GBI score was 23.4% lower for the CPC rinse group than for the placebo rinse group (0.072 *vs.* 0.094) and was highly statistically significant (P= 0.006) (Table 6).

For subjects in the Month 6 analysis, the baseline median GBI score for the CPC rinse group was 0.106 compared to 0.102 for the placebo rinse group. At Month 6, the median

Table 6. Gingival Bleeding Index results.

**Month 3 Analysis**

| Treatment | N | Baseline score (Mean ± SE) | Month 3 score (Adjusted Mean[a] ± SE) | % Reduction[b] |
|---|---|---|---|---|
| Placebo rinse | 64 | 0.122 ± 0.0080 | 0.094 ± 0.0056 | ------- |
| CPC rinse | 60 | 0.114 ± 0.0087 | 0.072 ± 0.0058 | 23.4% |

The adjusted means were statistically significantly different (P= 0.006).

**Month 6 Analysis**

| Treatment | N | Baseline score (Median ± IQR) | Month 6 score (Adjusted Median ± IQR) | % Reduction[c] |
|---|---|---|---|---|
| Placebo rinse | 62 | 0.102 ± 0.0648 | 0.060 ± 0.0796 | ------- |
| CPC rinse | 56 | 0.106 ± 0.0726 | 0.040 ± 0.0644 | 33.3% |

Based on a rank analysis of covariance, the treatments were statistically significantly different (P= 0.002).
[a] Adjusted means and standard errors from analysis of covariance with baseline score as the covariate.
[b] % Reduction = 100% x (Placebo rinse mean – CPC rinse mean)/Placebo Rinse mean.
[c] % Reduction = 100% x (Placebo Rinse median – CPC Rinse median)/ Placebo rinse median.

Table 8. Turesky Modified Quigley Hein Plaque Index results.

**Month 3 Analysis**

| Treatment | N | Baseline score (Mean ± SE) | Month 3 score (Adjusted Mean[a] ± SE) | % Reduction[b] |
|---|---|---|---|---|
| Placebo rinse | 64 | 2.69 ± 0.050 | 2.41 ± 0.053 | ------- |
| CPC rinse | 60 | 2.73 ± 0.056 | 1.93 ± 0.054 | 19.9% |

The adjusted means were statistically significantly different (P< 0.0001).

**Month 6 Analysis**

| Treatment | N | Baseline score (Mean ± SE) | Month 3 score (Adjusted Mean[a] ± SE) | % Reduction[b] |
|---|---|---|---|---|
| Placebo rinse | 62 | 2.68 ± 0.051 | 2.34 ± 0.051 | ------- |
| CPC rinse | 57 | 2.73 ± 0.058 | 1.97 ± 0.053 | 15.8% |

The adjusted means were statistically significantly different (P< 0.0001).
[a] Adjusted means and standard errors from analysis of covariance with baseline score as the covariate.
[b] % Reduction = 100% x (Placebo rinse mean – CPC rinse mean)/Placebo rinse mean.

GBI score was 33.3% lower for the CPC Rinse group than for the placebo rinse group (0.040 *vs.* 0.060) and was highly statistically significant (P= 0.002) (Table 6).

Efficacy results for the proportion of sites bleeding were similar to the GBI results. Specifically, the baseline mean proportion of sites bleeding was 0.101 for the CPC rinse group and 0.106 for the placebo rinse group among subjects examined at Month 3. The adjusted mean proportion of sites bleeding at Month 3 was 23.8% lower for the CPC rinse group than for the placebo rinse group (0.064 *vs.* 0.084) and was highly statistically significant (P= 0.006) (Table 7).

For subjects examined at Month 6, the baseline mean proportion of sites bleeding was 0.096 for the CPC rinse group and 0.105 for the placebo rinse group. At Month 6 the adjusted mean proportion of sites bleeding was 0.050 for the CPC rinse group compared to 0.074 for the placebo rinse group, or a 32.4% difference. The difference between groups

was highly statistically significant (P= 0.007) (Table 7).

*Plaque* - The baseline mean MQH score for subjects in the Month 3 analysis was 2.73 for the CPC rinse group and 2.69 for the placebo rinse group. At Month 3, the adjusted mean score for the CPC rinse group was 19.9% lower than that of the placebo rinse group (1.93 *vs.* 2.41). The difference between groups was highly statistically significant (P< 0.0001) (Table 8).

The baseline mean MQH scores for subjects in the Month 6 analysis were 2.73 for the CPC rinse group and 2.68 for the placebo rinse group. At Month 6 the adjusted mean for the CPC rinse group was 15.8% lower than that of the placebo rinse group (1.97 *vs.* 2.34). The difference between groups was highly statistically significant (P< 0.0001) (Table 8).

Neither treatment group had any significant adverse reactions or remarkable oral soft tissue findings related to mouthrinse use. One mild adverse event (angular cheilitis) was reported during the study in the CPC group and self-resolved.

## Discussion

Results of the study support the long-term antiplaque and antigingivitis benefits of a novel alcohol-free, high bioavailable[18] 0.07% CPC mouthrinse, further adding to the published evidence of efficacy of this therapeutic mouthrinse.[29-31] In this study, the CPC rinse reduced gingivitis and gingival bleeding by 15% and 33%, respectively, relative to placebo after 6 months usage. The proportion of bleeding sites was reduced by 32% relative to placebo. Statistically significant benefits were also observed for plaque.

Reports in the literature have consistently demonstrated that mouthwash rinsing is an important component of an oral care regimen. Many mouthwashes contain more than 21% alcohol, however, and may cause an unpleasant burning sensation. In addition, millions of patients prefer not to use alcohol-based products for reasons unrelated to product esthetics, including medical, religious, and age.

Patients with xerostomia, or dry mouth, are one group that can benefit from an alcohol-free therapeutic rinse. Xerostomia is the abnormal reduction of saliva. The condition can be a symptom of certain diseases or an adverse effect of certain medications. Over 400 medications are reported to cause a reduction in salivary gland production,[32] making xerostomia increasingly common among elderly patients who often take multiple medications.[33] The management of xerostomia principally consists of the avoidance of factors that might cause or aggravate dry mouth, the application of salivary substitutes, and the prevention of associated oral complications (*e.g.*, caries).[34] There is general consensus among dental professionals that these patients should avoid alcohol-based mouthwashes since they may worsen the dry mouth effect.[35-37] Crest Pro-Health Rinse offers therapeutic benefits to this group without the concern that alcohol will further exacerbate the symptoms. Other patient types may also prefer alcohol-free oral hygiene products, including diabetics, cancer patients, orthodontic patients, patients of certain religious faiths, and patients with a history of alcohol abuse.

In conclusion, this 6-month, randomized clinical trial shows Crest Pro-Health Rinse with high bioavailable CPC provides long-term gingival health benefits for the general population. The rinse may be particularly appealing to certain patients who prefer to use alcohol-free products.

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